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ABSTRACT

The relationship of bilirubin (a red bile pigment that is sometimes found in the urine and occurs in the blood and tissues in jaundice) in infancy to later intellectual development was investigated in 241 infants with moderately elevated and high bilirubin levels. Ss were administered motor, psycholinguistic, and intelligence tests at age 8 months, 4 years, and 7 years. High bilirubin levels were found to be significantly associated with decreased mental and motor development at 8 months of age. There were no significant differences on measures of intellectual development at 4 and 7 years of age. (A review of previous research on the subject is presented.) (SBH)

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The hypothesis that mental retardation may be a sequela of kernicterus has been substantiated by a number of investigators. However, an unresolved question remains regarding whether or not increased levels of serum bilirubin in the blood and tissues of the infant (a sign of impending kernicterus) without the manifestation of hemolytic disease or acute brain damage is a sufficient insult to depress the intellectual potential of the neonate. It has been postulated that if a continuum of reproductive casualty is operative in regard to bilirubin, increasing levels of this factor prior to the development of the classic signs of kernicterus should exert a progressively adverse effect on the subsequent intellectual development of the neonate.

Bilirubin is a red bile pigment that "is sometimes found in the urine and occurs in the blood and tissues in jaundice" (Dorland, 1965, p. 196). This chemical is deposited in the skin and other organs, especially the brain, which results in the yellow skin color typifing jaundice, technically known as hyperbilirubinemia. When the serum bilirubin levels rise to about 20-25 mg/100 ml of blood in the neonate, the condition is known as kernicterus (Robinson & Robinson, 1965). The classic syndrome of kernicterus in infancy is characterized by vomiting, persistently shrill crying, hypertonicity, respiratory difficulty, and inability to gain weight (Perlstein, 1950). If the neonate is not treated with blood transfusions, kernicterus is often fatal; survivors

are likely to suffer motor impairment, brain damage, and mental retardation (Robinson & Robinson, 1965).

Jaundice and kernicterus are well known sequelae of erythroblastosis fetalis which is "a hemolytic anemia of the fetus or newborn (e. neonatorum) caused by the transplacental transmission of maternally formed antibody, usually secondary to an incompatibility between the blood group of the mother and that of her offspring" (Dorland, 1965, p. 511). Approximately 90% of the cases of erythroblastosis fetalis are due to Rh incompatibility in which the Rh negative mother develops anti-Rh agglutinins in response to the transfusion of Rh positive blood from the fetus. If the anti-Rh agglutinins gain access to the fetus' circulatory system, the antibodies will destroy the red blood cells of the fetus, and it will develop anemia leading to anoxia since the red blood cells transport oxygen throughout the body (Gilmour, 1950).

It appears that there is a relationship between bilirubin concentrations and abnormal developmental status at eight and twelve months, but prediction beyond one year of age is extremely tentative at this time. Thus far few studies have been reported which assess the relationship between serum bilirubin concentrations and intellectual status at the preschool level and beyond. The Collaborative Project for the Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Childhood (Berendes, 1966) included several serum bilirubin determinations in their protocol for the assessment of the neonate. The purpose of this paper is to determine the relationship between serum bilirubin level in the neonate and subsequent intellectual development in one sample of Collaborative Project subjects.

Earlier research regarding the effects of increasing levels of serum bilirubin in the neonate on subsequent intellectual development found that the primary etiologic factor in cases of increased levels of bilirubin was Rh incompatibility between the mother and her fetus. Yannet and Lieberman (1944) were among the first to suggest that iso-immunization of the Rh factor in the Rh negative mother, without evidence of the clinical syndrome of kernicterus in the neonate, was a sufficient insult to retard mental development in children so affected. They also suggested (1945) that A and B blood group incompatibility between the mother and fetus was a factor leading to increased incidence of mental retardation. Evidence was obtained by comparing the blood types of inmates of a training school for the mentally retarded with the blood types of their mothers. Among inmates, in which no specific etiologic agent of retardation was known, there was a significant increase of Rh, and A and B blood type incompatibility.

However, later studies by Gilmour (1950) and Zwerling, Gold, Jervis, and Ginsberg (1951) failed to confirm that maternal iso-immunization, without signs of hemolytic disease or brain damage, is a potential etiologic factor in mental retardation.

Several studies have investigated the relationship between neonatal hyperbilirubinemia accompanied by kernicterus and subsequent mental development. Lande (1948) reviewed the case histories of eight subjects who evidenced clinical kernicterus at birth; the oldest subject was 11 1/2 years old at the time of investigation. Lande found that mental development among her subjects was markedly retarded from

birth and soon came to a complete standstill. This resulted in a rapidly declining IQ with advancing age. She found however no correlation between the degree of jaundice or anemia and the degree of mental retardation.

Gerver and Day (1950) investigated the extent of mental impairment in subjects who had recovered from erythroblastosis fetalis without accompanying motor impairment, because it was held that individuals who had recovered from kernicterus without evidence of motor disability would develop normally. The 68 subjects in their experimental group met the following criteria: (a) clinical diagnosis of erythroblastosis fetalis; (b) jaundice (hyperbilirubinemia); (c) anemia to the extent that administration of blood was required; and (d) evidence that the condition was due to blood incompatibility. The control group was composed of older, unaffected siblings of the experimental subjects. Results of the Stanford-Binet revealed a significant mean IQ difference of 11.8 points ($p<.001$) between the experimental and control groups (mean IQ scores of 102.7 and 114.5, respectively). There were no significant IQ differences between the two groups due to sex, birth weight, or age inequities. Gerver and Day concluded that some factor, probably the erythroblastosis fetalis, caused a widespread and usually moderate lowering of intelligence of affected children.

Day and Haines (1954) later replicated the Gerver and Day study. They found a 6.1 point difference in mean Stanford-Binet IQ ($p<.01$) between the 68 experimental subjects and the control group of older 68 siblings (mean IQ scores of 106.5 and 112.6, respectively). The experimental group was then divided into those subjects who had

received blood transfusions (n=41) and those who had been given no blood or only one or more small transfusions (n=27). When compared to the control group the average IQ deficit of the first group, who had received blood transfusions, was 5.7 points, while the second, untreated group had an average IQ deficit of 6.7 points. Day and Haines suggested the 6.1 point difference between the IQ deficit of the experimental group as a whole found by them and the 11.8 point difference found by Gerver and Day (1950) may be due to the fact that no subjects in the earlier Gerver and Day study received blood transfusions, while 60% of the subjects in the Day and Haines study received some form of blood transfusion, though differences between mean IQ deficits found in the two studies were not statistically significant.

Day and Haines also divided the experimental group into those considered severely jaundiced (n=19) on the basis of total bilirubin level, and those considered minimally jaundiced (n=49). The severely jaundiced group's average IQ was 14.5 points lower than that of the control group, while the minimally jaundiced group had only a 2.5 point deficit ($p<.04$). They concluded that the degree of jaundice appeared to be significantly related to the extent of the IQ deficit.

Van Camp (1964) also examined the relationship between hyperbilirubinemia and intellectual development. The sample of 51 experimental subjects included children who exhibited neonatal jaundice; the control group included 49 subjects who did not evidence neonatal jaundice. A significant difference ($p<.025$) was found between the experimental group (mean IQ of 102.7) and the control group (mean IQ of 110.2) on

the Stanford Binet. Van Camp further subdivided the experimental group into those subjects who evidenced severe symptoms related to neonatal jaundice (bilirubin level of 21 mg % + 3 other diagnostic variables), and those subjects who had suffered less severe symptoms. The mean IQ of the group with less severe symptoms was 105.6, while the mean IQ of the group with more severe symptoms was 90.6 ($p<.005$). Van Camp concluded that the effects of hyperbilirubinemia were manifested in a continuum of reproductive casualty, with mild to moderate symptoms related to minor intellectual impairment and more severe symptoms associated with severe damage and sometimes resulting in death.

It has been generally accepted that an association exists between neonatal hyperbilirubinemia and kernicterus, and that mental retardation could be a sequela of kernicterus. In more recent times interest has focused on determining whether or not there exists a direct relationship between increasing levels of bilirubin and progressive deficits in mental functioning, as had been suggested by Day and Haines (1954); and by Van Camp (1964).

A number of studies have attempted to determine the relationship between varying levels of serum bilirubin, in the abasence of hemolytic disease or acute brain damage, and subsequent mental functioning.

Johnston, Angara, Baumal, Hawke, Johnson, Keet, and Wood (1967) conducted a five year follow-up study of 168 subjects who had neonatal serum bilirubin determinations of over 20 mg %. Between the ages of five and six, 129 of the original subjects and 82 older unaffected siblings, who composed the control group, were administered the Stanford Binet. The difference between the experimental group's mean IQ of 104.8

and the control group's mean IQ of 102.8 was not significant. Johnston, et al (1967) therefore concluded that mental retardation does not appear to be a sequela of hyperbilirubinemia in the absence of clinical signs of kernicterus.

Odell, Storey, and Rosenberg (1970) also conducted a follow-up study of subjects who had neonatal jaundice but who had not shown physical signs of classic kernicterus. Between the ages of four and seven, 32 subjects were administered psychometric tests. The Stanford-Binet was administered to subjects who were less than five years of age, and the Wechsler Intelligence Scale for Children (WISC) was given to subjects five years of age or older. The intelligence continuum was dichotomized into normal and abnormal with IQ scores of less than 80 considered to be abnormal. Chi square tests were used to determine whether or not there was a relationship between IQ and highest level of bilirubin concentration. Odell, et al (1970) found no statistically significant relationships between the highest bilirubin concentrations and IQ, dichotomized as abnormal and normal. Several methodological problems were considered by the authors. They suggested that if the entire IQ continuum had been utilized instead of dichotomizing it into abnormal and normal, and if comparisons had been made between the subjects and unaffected controls instead of just within the jaundiced group, results may have revealed that abnormally high concentrations of bilirubin during the neonatal period were associated with deficits in intellectual functioning. But, on the basis of the findings of this study, Odell and his associates concluded that there appeared to be no correlation between maximum serum bilirubin concentrations, in the absence of hemolytic disease, and later intellectual functioning.

Upadhyay (1971) conducted a study through the Johns Hopkins section of the Collaborative Project to determine the risk of long-range neurological impairment in a group of full-term neonates whose maximum serum bilirubin level was in excess of 20 mg %, in comparison with controls who were matched for race, sex, maternal age, socioeconomic status, date of birth, and birth weight, but whose maximum bilirubin level remained below 20 mg %. Several follow-up examinations were administered to the experimental group of 20 subjects and their controls including a 4-month pediatric examination; the 8-month Bayley examination; a 12-month neurological examination; a 36-month language, hearing and speech examination; and finally, 48-month psychometric examinations including the Stanford-Binet. Results indicated significant differences ($p<.01$) between the number of experimental group children who were rated as suspect or abnormal on the 8-month Bayley tests and the 48-month psychological test battery, and the number of control group children so rated, but no significant difference between the mean Binet IQ of 93.5 attained by the experimental group and the 90.5 mean IQ of the control group. Upadhyay concluded that excessively high serum bilirubin levels, without evidence of kernicterus, does not adversely influence mental functioning; however, children who experience high bilirubin levels during the neonatal period may evidence differences from normal children in other realms of psychological functioning.

Other studies based on Collaborative Project data which have investigated the association of serum bilirubin levels during the neonatal period and later development have found results which appear to be in concordance with those of Upadhyay. Boggs, Hardy and Frazier

(1967) in a preliminary report combining data from all Collaborative Project institutions reported the correlation, when controlling for birth weight and Apgar score, between maximum neonatal serum bilirubin concentration and developmental status at eight months using the Bayley Mental and Motor Scales for 23,000 single, viable infants. A score of 75 or less on the Mental Scale, and a score of 27 or less on the Motor Scale was considered abnormal. Results indicated a highly significant association ($p<.005$) within each weight group (<2000 gms; 2001-2500 gms; 2501-3000 gms; $\geq$3001 gms) between bilirubin level and 8-month abnormal mental and motor scores. It appeared that as the birth weight declined the number of subjects diagnosed as abnormal on the mental and motor tests increased. There also appeared to be a similar relationship between low Apgar scores (<7) and deficit on the mental and motor tests. Boggs, et al (1967) concluded there appeared to be a significant relationship between high serum bilirubin levels and abnormal mental and motor scores at eight months. Additionally, they maintained that distress at birth, as measured by the Apgar Index, and low birth weight are further insults superimposed on the relationship between bilirubin and 8-month developmental scores.

Hardy and Peeples (1971) extended the period of assessment by evaluating the association between bilirubin levels and neurological abnormalities diagnosed through the end of the first year of the infant's life. They observed 3,955 participants in the Johns Hopkins Collaborative Study for whom they had serum bilirubin determinations during the neonatal period, and either 8-month Bayley mental and motor test scores or the 12-month pediatric neurological examination. Results

indicated significant differences between maximum bilirubin levels recorded for the different weight groups. Of the neonates who had birth weights of 2,500 gms or less, 44% had maximum bilirubin levels of $\geq$10 mg %, while only 13% of neonates weighing more than 2,500 gms had bilirubin levels which exceeded 10 mg %. When gestational age was dichotomized into less than 37 weeks and 37 weeks or more, the results were similar to those found in the birth weight distribution. Neonates with gestational age at birth of less than 37 weeks showed significantly higher bilirubin levels. The inverse relationship between bilirubin levels and Bayley test scores was similar to that reported by Boggs and his associates (1967).

Hardy and Peeples also found that the percentage of children rated as normal on the 12-month neurological examination decreased as the total serum bilirubin level increased and that this association became more discernable as the bilirubin level exceeded 10 mg %. Again, Hardy and Peeples reached conclusions that were similar to those reported by Boggs, et al. Primarily, Hardy and Peeples proposed that there is a relationship between maximum serum bilirubin levels and neurological abnormalities diagnosed at twelve months. They maintained that low birth weight and attenuated gestational period serve as additional insults acting in a cumulative manner to futher strengthen the primary association between bilirubin level and neurological status at 12 months.

In summary, it is generally accepted that mental retardation may be a sequela of kernicterus so that infants who suffer from hyperbilirubinemia and kernicterus during the neonatal period appear to have a poor prognosis of later development. Recent studies have attempted to assess the

relationship between advanced levels of bilirubin, in the absence of hemolytic disease, and later development.

Method

Sample

Subjects were born at the University of Minnesota Hospitals between 1960 and 1964 and were participants both in the Educational Follow-Up Project (Balow, Anderson, Reynolds & Rubin, 1959), a continuing longitudinal study of the sequelae of perinatal and early childhood conditions, and the Minnesota section of the Collaborative Perinatal Research Project.

The sample for the present study was drawn from Educational Follow-Up Project (EFUP) subjects for whom neonatal bilirubin determinations were available (n = 1516). Total serum bilirubin levels of study subjects ranged from 0-23 mg %. It is generally accepted (Diamond, Allen, Vann, & Powers, 1952) that bilirubin levels of 0-10 mg % fall within the "normal" range, while previous research (Boggs et al., 1967) had determined a critical threshold of 16-19 mg % beyond which depressed mental and motor development become more likely. Included in the present investigation were all EFUP subjects with maximum bilirubin levels of 11 mg % or above, a total of 241 subjects (15.9% of the total EFUP population). Of these 241 subjects, 164 had bilirubin levels ranging from 11 to 15 mg % and were classified as the "Moderately elevated" group, while 77 subjects had bilirubin levels ranging from 16 to a high of 23 mg % and were classified as the "High" bilirubin group. A control group of 130 subjects with normal bilirubin levels

(0-10 mg %) was randomly drawn from the remainder of the study population and designated as the "Low" bilirubin group.

Measures[1]

A serum bilirubin determination was done on each infant between 36-60 hours of age, centering around 48 hours of age. If the total bilirubin level was ≥10 mg % the test was repeated in 24 hours, and if the level continued to be over 10 mg %, a third test was done at 4-5 days. The value used in this study was the maximum total serum bilirubin concentration, regardless of age.

The Bayley Scales of Mental and Motor Development (Collaborative Study Manual, Research Form, 1961) were administered to the infants at eight months of age. The Mental Scale measures responses involving social interaction, manipulation of articles, imitation, and responses to visual and auditory stimuli, while the Motor Scale measures progressions of gross motor (i.e., sitting, standing, climbing) as well as fine motor (i.e., grasping objects of various sizes) abilities. On the Mental Scale a score of 75 or below, and on the Motor Scale a score of 27 or below, was considered suspect.

At four years of age the subjects were administered the Stanford-Binet, Short Form L-M. At ages five (pre-kindergarten) and six (pre-first grade) subjects were individually administered measures of school

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[1]Neonatal, neurological, and psychological examinations were administered at the University of Minnesota Hospitals and made available through the cooperation of the Collaborative Project. Information on school readiness, language development, and school progress was obtained as part of the continuing data collection activities of the Educational Follow-Up Project.

readiness and language development. The Metropolitan Readiness Tests (MRT) (Hildreth, Griffiths, & McGauvran, 1965), was designed to measure skills and abilities contributing to readiness for initial first grade work, such as auditory and visual perception, motor coordination, linguistic skills, knowledge of numbers, and ability to attend to and follow directions. The Illinois Test of Psycholinguistic Abilities (ITPA) (McCarthy & Kirk, 1961), was designed to measure specific aspects of psycholinguistic abilities in the areas of encoding, decoding, associating, and sequencing.

At age seven subjects were administered the Wechsler Intelligence Scale for Children (WISC). The WISC yields Verbal, Performance, and Full Scale IQ scores.

Analysis

Mean scores of High, Moderate and Low bilirubin groups on standardized measures of development were compared through one-way analysis of variance procedures. Since data were not available for all subjects on all measures, the Ns vary slightly at different age levels. When the analysis of variance revealed significant mean differences among the three bilirubin groups on a specific measure, a further analysis using the Newman-Keuls (Bruning & Kintz, 1968) was employed to determine the significance of the difference between pairs of bilirubin groups on that same measure (e.g., differences between the Low and the Moderate groups and between the Moderate and the High groups on the Bayley Scale of Mental Development).

Results

Insert Table 1 about here

Table 1 presents means and standard deviations of the three bilirubin groups on measures of infant development, intelligence, school readiness and language development. Significant differences were found favoring low over high bilirubin groups on both the Bayley Mental ($p < .01$) and Motor ($p < .03$) scales at 8 months. However, no significant differences were found between bilirubin groups on the 4-year Binet, the 7-year WISC, the 5- and 6-year administrations of the MRT or the 5- and 6-year administrations of the ITPA.

Further analysis using the Newman-Keuls test showed significant differences between the high and low bilirubin groups but not between the high and the moderate, nor between the moderate and low groups on the Mental Scale. On the Motor Scale significant differences were found between groups of high and moderate as well as between high and low bilirubin, but not between moderate and low bilirubin groups.

Discussion

High bilirubin levels were found to be significantly associated with decreased mental and motor development at eight months of age. As the bilirubin level increased, scores on the Bayley Scales decreased. These findings were consistent with those reported by Boggs, et al. (1967) and by Hardy & Peeples (1971).

There were no significant differences on measures of intellectual development at four and at seven years of age, which is consistent with previously reported studies in which subjects were tested at approximately four years of age with the Stanford-Binet (Johnston, et al. 1967; Odell, et al. 1970; Upadhyay, 1971). However, the present findings differed with those reported by Day and Haines (1954) and by Van Camp (1964). It should be noted that experimental subjects in the Day and Haines study were subdivided into "severe" and "less severe" groups on the basis of five variables (one of which was neonatal bilirubin level) each of which themselves were associated with mean differences in IQ scores. Indeed there was considerable overlap in bilirubin levels between subjects in the "severe" and "less severe" groups. Therefore, the IQ difference found between the two groups might possibly be attributable to variables other than bilirubin level which led to their original classification.

Thus it appears that there is an early developmental deficit associated with elevated neonatal bilirubin levels, but this study failed to support the hypothesis that elevated bilirubin levels, in the absence of other signs of severe distress, are predictive of long-term intellectual deficits.

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Table 1

Mean Scores on Measures of Mental and Motor Development of Subjects with Low, Moderate, and High Bilirubin Levels

Measures	Low Bilirubin (0-10 mg %)			Moderate Bilirubin (11-15 mg %)			High Bilirubin (16-23 mg %)			
	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	p*
8-mo Bayley Mental	120	79.63	4.80	153	78.31	6.25	66	76.61	9.85	.01
8-mo Bayley Motor	120	33.82	4.27	153	33.63	5.29	66	31.88	5.43	.03
4-yr Binet	118	102.20	16.23	153	103.69	16.85	72	101.78	17.83	NS
7-yr WISC - VIQ	114	100.06	12.74	141	101.75	13.79	62	102.02	15.01	NS
Pre-K MRT	99	28.87	14.18	125	28.66	14.61	56	27.88	15.28	NS
Pre-K ITPA	99	58.62	11.63	126	57.24	11.60	59	57.24	14.41	NS
Pre-1st MRT	111	53.87	17.27	126	54.23	17.25	50	54.02	18.94	NS
Pre-1st ITPA	110	72.01	10.61	126	73.82	11.60	50	74.22	13.68	NS

*p = level of significance